MULTIREGRESSION DYNAMIC MODELS IN GROUP ANALYSIS

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Abstract

Connectivity studies of the brain are usually based on functional Magnetic Resonance Imaging (fMRI) experiments involving many subjects. These studies need to take into account not only the interaction between areas of a single brain but also the differences amongst those subjects. This work uses the group-structure (GS) approach applied to Multiregression Dynamic Model (MDM), as defined in Costa *et al.* (2019), to study the information flow of the brain.

The GS approach consists of grouping subjects according to the similarities in their graph structures. For this, firstly the process of learning network is done twice: a) for each subject individually and b) for each pairwise of subjects under the constraints of both individuals have the same graphical structure but the connectivity strength may be different. To search over networks we have used an efficient search-and-score method called as MDM-IP algorithm (Costa *et al.*, 2015) which is based on the *gobnilp* system (Cussens, 2011; Bartlett and Cussens, 2013) and the scores were defined as the joint log predictive likelihood (LPL) calculated as

$$\text{LPL}_i(m) = \sum_{r=1}^{n} \sum_{t=1}^{T} \log p_{tr}(y_{it}(r)|\mathbf{y}_i^{t-1}, Pa_i(r), m), \tag{1}$$

where this conditional forecast distribution has the closed form of a students t-distribution (Costa *et al.*, 2015), m denotes the current choice of model that determines the relationship between the n regions expressed graphically through the underlying graph, the column vector $\mathbf{Y}'_{it} = (Y_{it}(1), \ldots, Y_{it}(n))$ denotes the data from n regions at time t for subject i and their observed values designated respectively by $\mathbf{y}'_{it} = (y_{it}(1), \ldots, y_{it}(n))$, the time series until time t for region $r = 1, \ldots, n$ is defined as $\mathbf{Y}^{it}(r)' = (Y_{i1}(r), \ldots, Y_{it}(r))$ and $Pa_i(r)$ is the parent set of $Y_{it}(r)$.

Secondly, a separation measure, $d(i,j)$, is calculated as the difference between the individual networks, M_i, and the pairwise group network, m_G, for every pair of subjects i and j, *i.e.*

$$d(i,j) = \text{LPL}_i(M_i) + \text{LPL}_j(M_j) - \text{LPL}_i(m_G) - \text{LPL}_j(m_G),$$

where $i \in \{1, \ldots, S-1\}$, $j \in \{2, \ldots, S\}$, $j > i$. So here the individual networks, M_i, are estimated by maximising the scores in equation (1) in the stage a whilst the pairwise

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group networks, m_G, is then estimated by maximising the sum of scores for only two subjects, i and j in the stage b of learning network process cited above.

After that, subjects with similar networks are grouped using this separation measure and a cluster analysis. Then a new graphical structure is estimated for each one of subgroups by maximising the sum of scores for subjects belonging to the same subgroup. Finally, the connectivity strengths are estimated per subgroup using the MDM.

Here the GS approach is compared to other three group analysis approaches easily found in the neuroimaging literature (*e.g.* Mechelli *et al.*, 2002; Li *et al.*, 2008; Ramsey *et al.*, 2010; Gates and Molenaar, 2012). The first approach is the virtual-typical-subject (VTS) which creates a typical subject calculating the average of observed variables for every node over subjects or concatenating the datasets. In this way, the usual MDM can be used to estimate the network for this single individual. A second method is the common-structure (CS) that estimates the same network structure but allows the connectivity strength to differ between subjects. Then the group network structure is found by maximising the sum of scores LPL_i for all individuals and connectivity strength is estimated as the average of the smoothed estimates of this parameter over subjects. In contrast, the third method of group analysis, individual-structure (IS), usually learns individual networks independently, using the individual scores as in equation 1, and then the group network structure consists of the edges that exist in the individual network for most subjects. After that, the MDM is fitted for all subjects considering this group structure and, as the CS approach, the average of the smoothed estimates over all individuals defines connectivity strength. For more discussion of these methods see *e.g.* Costa *et al.* (2019), Oates (2013), Gates and Molenaar (2012) and Kherif et al. (2004).

Firstly we compared the four group analysis approaches described above using synthetic data. The aim was to assess the efficacy of methods when subjects are sampled from populations whose individuals may exhibit different networks. We then simulated data from 3 different DAGs (DAG1, DAG2 and DAG3), 10 subjects for each DAG, and considering 4 nodes and 197 time points. The pairwise logBF separation for all pairs of subjects was evaluated as shown above and considering the MDM-IPA. In order to assess the homogeneity of this group, we used *the hierarchical cluster* (Everitt *et al.*, 2011, Chapter 4) and the *multidimensional scaling* (MDS; Everitt *et al.*, 2011, Section 2.3.3). The hierarchical cluster results can be illustrated through a *dendrogram* and, to define subgroups, we use the *dynamic tree cut* (hybrid algorithm; Langfelder *et al.*, 2008). The hybrid algorithm correctly identified the number of subgroups and most of the subjects were correctly grouped. The criteria of logBF ≥ 2 showed strong evidence for the first model used in its calculation (West and Harrison, 1997). It should be remembered that in the calculation of $d(i,j)$ in the first model, individual DAGs were estimated independently. Therefore, because the average separation between subjects belonging to the same group was around 1.8, this result indicates that these subjects are likely to share the same network structure. In contrast, the average separation between groups was almost 30. This provides strong evidence that people from different subgroups have different graphical structures.

After that we applied the GS approach into a real resting-state fMRI data with 3 levels: brain, session and subject. The application consisted of a resting-state study in which participants were instructed to rest with their eyes open while the word "Relax" was centrally projected in white, against a black background (Shehzad *et al.*, 2009; Ridgway *et al.*, 2013). There are 25 right-handed native English-speaking participants, being 11 males with mean age of 20.5 ± 8.4. Subjects had no history of psychiatric or neurological illness, as confirmed by a psychiatric clinical assessment. They were scanned 3 times, being session 2 was between 5 and 11 months after the first, and session 3 was less than 45 minutes after session 2. Data consist of 197 BOLD fMRI

resting-state time-points, sampled every 2 seconds, for 4 ROI's: Posterior Cingulate - *PC*; Anterior Frontal - *AF*; Left Lateral Parietal - *LP* and Right Lateral Parietal - *RP*. According to Shehzad *et al.* (2009), "Mean time series for each ROI were extracted from this standardized functional volume by averaging over all voxels within the region. To ensure that each time series represented regionally specific neural activity, in each analysis, the mean time series of each ROI was orthogonalized with respect to 9 nuisance signals (global signal, white matter, cerebrospinal fluid, and 6 motion parameters)". These data are available for download in http://www.nitrc.org/projects/nyu_trt

In this experiment, we are interested to study the information flow of the brain, and then we need to estimate the map of brain connectivity. First, four different graphical structures were manually chosen to representing the scientific beliefs about the brain connectivities (from RS-DAG1 to RS-DAG4). RS-DAG1 understands that the Posterior Cingulate hub drives the other regions whilst RS-DAG2 understands that the Posterior Cingulate hub is driven by the Anterior Frontal and the Left and the Right Lateral Parietal. In RS-DAG3, the information flows forward while in RS-DAG4 the information flows backwards. Comparing these 4 DAGs, the graphical structure that maximises the log predictive likelihood was selected for each dataset using the MDM. The RS-DAG4 was chosen for most of the datasets (almost 55%), followed by RS-DAG1 for about 40%. Then a group analysis was applied without giving preference to any specified model. Broadly speaking, the results of the search process were consistent with scientific knowledge.

Graphical structures were estimated for the VTS, the CS and the IS approaches, considering the 75 datasets and the MDM. As expected, the result of the IS approach was RS-DAG4. This was the graph chosen for most subjects. In contrast to the simulation study, VTS showed a plausible result which was close to RS-DAG4. The CS approach also provided a consistent result with the first learning network process, *i.e.* the information in these brain regions flows backwards. However, the directionality of the connection between *RP* and *PC* regions was contrary to what was expected. We noted that none of the methods identified two different graphical structures in this population.

For the sake of simplicity, we are assuming that all sessions share the same graphical structure and then the GS approach was applied for 25 subjects, summing the scores over the sessions. The hybrid algorithm suggested two subgroups (orange and blue). The scores of the subjects who belong to the same subgroup were summed and then the MDM-IPA was applied to each subgroup independently. We noted that the estimated graph of the GS-subgroup2 is similar to RS-DAG4 whilst the GS-subgroup1 is similar to RS-DAG1. Therefore, in contrast to the other methods, the result of the GS approach was consistent with the previous analysis that showed evidence of two different subgroup networks. The logBF comparing heterogeneous with homogenous group was found to be around 118. This provided strong evidence for a model in which subjects were clustered into at least two subgroups.

References

Bartlett M., Cussen J. (2013). Advances in Bayesian network learning using integer programming. In *Proceedings of the 29th Conference on Uncertainty in Artificial Intelligence (UAI 2013)*. AUAI Press. To appear.

Costa L., Smith J., Nichols T., Cussens J., Duff E.P., Makin T.R. (2015). Searching multiregression dynamic models of resting-state fMRI networks using integer programming. *Bayesian Analysis*, 10(2), 441-478.

Costa L, James Q. Smith, and Thomas Nichols. "A group analysis using the Multire-gression Dynamic Models for fMRI networked time series." Journal of statistical planning and inference 198 (2019): 43-61.

Cussens J. (2011). Bayesian network learning with cutting planes. In Fabio G. Cozman and Avi Pfeffer, editors, Proceedings of the 27th Conference on Uncertainty in Artificial Intelligence (UAI 2011), pages 153-160, Barcelona. AUAI Press.

Everitt B., Landau S., Leese M., Stahl D. (2011). *Cluster analysis*. 5th ed. Chichester: Wiley.

Gates, K. M. (2012). Identifying subgroups using fMRI connectivity maps. Paper presented at the annual meeting for the Society for Neuroscience, New Orleans

Gates, K. M., Molenaar P. C. M. (2012). Group search algorithm recovers effective connectivity maps for individuals in homogeneous and heterogeneous samples. *NeuroImage*, 63, 310-319.

Gonçalves, M.S., Hall D.A., Johnsrude I.S., Haggard M.P. (2001). Can meaningful effective connectivities be obtained between auditory cortical regions? *NeuroImage*, 14, pp. 1353-1360.

Kherif F., Poline J.-B., Mériaux S., Benali H., Flandin G., Brett M. (2004). Group analysis in functional neuroimaging: selecting subjects using similarity measures. *NeuroImage*, 20 (4), pp. 2197-2208.

Langfelder P., Zhang B., Horvath S. (2008). Defining clusters from a hierarchical cluster tree: the Dynamic Tree Cut package for R. *Bioinformatics* 24(5), 719-720.

Li J., Wang, Z.J., Palmer, S.J., McKeown, M.J. (2008). Dynamic Bayesian network modeling of fMRI: a comparison of group-analysis methods. Neuroimage 41: 2. 398-407 Jun.

McGonigle D.J., Howseman A.M., Athwal B.S., Friston K.J., Frackowiak R.S., Holmes A.P. (2000). Variability in fMRI: an examination of intersession differences. *NeuroImage*, 11, 708-734.

Mechelli A., Penny, W.D., Price, C.J., Gitelman, D.R., Friston, K.J. (2002). Effective connectivity and intersubject variability: using a multisubject network to test differences and commonalities. NeuroImage 17 (3), 1459-1469 (11).

Oates C.J. (2013). *Bayesian Inference for Protein Signalling Networks*. PhD Thesis. Chapter 4. The University of Warwick: U.K.

Rajapakse J.C., Zhou J. (2007). Learning effective brain connectivity with dynamic Bayesian networks. *NeuroImage* 37, 749-760.

Ramsey J.D., Hanson S.J., Hanson C., Halchenko Y.O., Poldrack R.A., Glymour C. (2010). Six Problems for Causal Inference from fMRI. *NeuroImage*, 49: 1545-1558.

Salimi-Khorshidi G., Douaud G., Beckmann C.F., Glasser M.F., Griffanti L., Smith S.M. (2014). Automatic Denoising of Functional MRI Data: Combining Independent Component Analysis and Hierarchical Fusion of Classifiers. *NeuroImage*, 90, 449-468.

Sugihara G., Kaminaga T., Sugishita M. (2006). Interindividual uniformity and variety of the "Writing center": A functional MRI study. *NeuroImage*, 32, 1837-1849.

West M., and Harrison P.J. (1997). Bayesian Forecasting and Dynamic Models (2nd ed.) Springer-Verlag. New York.

Zheng X., and Rajapakse J.C. (2006). Learning functional structure from fMR images. *NeuroImage*, vol. 31, no. 4, pp. 16011613, July.

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